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FOREWORD

The Office of Health Technology Assessment (OHTA) evaluates the safety and effectiveness of new or unestablished medical technologies that are being considered for coverage under Medicare. These assessments are done at the request of DHHS' Health Care Financing Administration (HCFA), which uses them in support of medicare policy and decisionmaking.

Questions about Medicare coverage for certain health care technologies are directed to HCFA by such interested parties as insurers, manufacturers, Medicare contractors, and practitioners. Those of a medical, scientific, or technical nature are formally referred to OHTA for assessment.

OHTA's assessment activities include a comprehensive review of the medical literature and emphasize broad and open participation from within and outside the Federal Government. A range of expert advice is obtained by widely publicizing plans for input from Federal agencies, medical specialty societies, insurers, and manufacturers. The involvement of these experts helps assure the experience and varying viewpoints needed to round out the data derived from individual scientific studies and medical specialty analyses.

After OHTA receives information from experts and the scientific literature, the results are incorporated and synthesized into an assessment report. The Health Technology Assessment Reports form the basis for OHTA's communication to HCFA and are widely disseminated.

OHTA is part of the National Center for Health Services Research and Health Care Technology Assessment, Office of the Assistant Secretary for Health, Public Health Service, DHHS.

Enrique D. Carter, M.D.
Director Office of Health
Technology Assessment

John E. Marshall, Ph.D.
Director, National Center for
Health Services Research and Health
Care Technology Assessment

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Public Health Service Assessment

Apheresis in the Treatment of Guillain-Barre Syndrome

1985

INTRODUCTION

Apheresis is a technique which permits the selective removal of plasma or other blood components from the circulation. The primary use of apheresis has been to collect platelets or leucocytes from normal donors to be transfused into patients with specific blood product deficiencies. Apheresis has been used therapeutically in the treatment of several diseases such as hyperviscosity and thrombocytosis, in which specific substances can be identified and removed (1). Apheresis has also been used with success in the management of some autoimmune diseases such as Goodpasture's syndrome. It has been investigated in other diseases such as Guillain-Barre Syndrome, myasthenia gravis, lupus erythematosus, dermatomyositis and chronic relapsing polyneuropathy in which the clinical manifestations are associated with circulating immune complexes (2). The procedure commonly requires a blood processing machine. The machine pumps anticoagulated venous blood through an extracorporeal circuit into a centrifuge type cell separator (3). More recently, devices using filtration via semipermeable membranes or affinity columns have also been applied to apheresis (4,5). These techniques require identification of the specific plasma constituents to be removed (6). Commercially available cell separators used for apheresis utilize either continuous or intermittent flow centrifugation. The continuous flow systems allow constant withdrawal of small volumes of blood from the patient. Blood components are separated and selected fractions

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reinfused. The desired components are infused into the patient. The intermittent systems require a predetermined amount of blood to be withdrawn to fill the centrifuge bowl. This blood is differentially centrifuged and then reinfused into the patient (7). Depending on the device used, plasma, macromolecules and/or formed elements in the blood such as lymphoctyes can also be removed. Blood and appropriate isovolemic and isotonic fluids are then reinfused into the patient. The most commonly used replacement solutions are cystalloids, normal serum albumin, plasma protein fractions and fresh frozen plasma (8). Both albumin and fresh frozen plasma are associated with risks for acquiring viral hepatitis or other viral infections such as CMV and AIDS (9).

Apheresis is being performed in various inpatient and outpatient settings including hospitals, dialysis centers, blood banks and physicians' offices (10). Although standardized procedures for apheresis do not exist, the process commonly involves the transfer of 1-1.5 patient plasma volumes. It takes an average of 2-4 hours, and is usually repeated, daily or on alternate days. The frequency of treatment is determined by the type and severity of the disease being treated (11). In 1981 approximately 50,000 apheresis procedures were performed in the United States and more than 3,000 throughout Europe, Japan, and Canada in the treatment of more than 50 different diseases of varied etiologies. Apheresis is used most often for diseases that are presumed to be immunologically mediated and that do not respond to other conventional treatments (12).

BACKGROUND

Guillain-Barre Syndrome (GBS) is an acute demyelinating polyneuropathy characterized by a symmetrical ascending paralysis. It begins with weakness and paresthesias in the legs and progresses proximally to complete tetraplegia (13). The full blown syndrome may progress to include pseudobulbar palsy and diaphragmatic

paralysis. The motor weakness generally develops rapidly over the course of a few days and usually peaks by 3-4 weeks after onset. Cranial nerve involvement affects 50 percent of patients and is manifested by facial, extraocular muscle and tongue weakness. Respiratory involvement may be severe enough to require mechanically assisted ventilation for prolonged periods. This may occur in 10-25 percent of patients (14,15).

GBS can affect all age groups (median age, 48) and has a mean annual incidence of 1-2/100,000 (16,17). Although the etiology of the disease is unknown, it is commonly preceded by viral illnesses or other systemic insults. Leneman in a review of 1,100 cases, was able to identify an episode of infectious disease in the month prior to the onset of GBS in approximately 60 percent of cases (18). No recognizable antecedent event was identified in three percent of cases. In ten percent of the cases miscellaneous events such as vaccinations, surgery, immune disorders, pregnancy, malignancies and endocrinopathies were perceived as related to onset.

A spontaneous and complete recovery is seen in approximately 60 percent of patients beginning 2-4 weeks after the progression of paralysis has ceased. In 20-40 percent of patients the recovery is incomplete and a residual disability persists. Relapse is seen in 5-10 percent of patients and there is an overall mortality of 5-6 percent (19,20,21).

Respiratory failure is the most serious life-threatening complication of GBS. In a series of 79 patients with GBS seen at the Mayo Clinic during a six year period, 16 percent required mechanical ventilation lasting 7-93 days (22). In a study of 38 fatal cases of GBS, most deaths followed medical complications including respiratory paralysis, pneumonia, arrhythmias, pulmonary emboli and pneumothorax. Eighty percent of the deaths were sudden (23).

The pathologic lesions characteristic of GBS consist of circumscribed areas of segmental demyelination of peripheral nerves in association with lymphocytic and

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macrophage infiltration (24,25,26). The pathogenesis of specific lesions is unexplained. However, autoimmune mechanisms are believed to be involved (27,28,29). Humoral mechanisms have been hypothesized by the finding of immunoglobulin in nerves. Circulating immune complexes and complement fixing antibodies against neural tissue are found in the majority of patients with GBS. Cell-mediated mechanisms have been implicated by the presence of activated lymphocytes in patients with GBS which are felt to cause sensitization of lymphocytes to peripheral nerve myelin preparations.

The hypothesis that there is an autoimmune mechanism underlying GBS rests, in part, on the similarities between clinical GBS and experimental allergic neuritis (EAN). The latter is produced by injection of animals with preparations of peripheral nerve. Both diseases exhibit similar clinical signs and the common pathological denominator of an inflammatory demyelinative neuritis (28,30).

Although immunologically mediated myelin destruction is generally regarded as the pathophysiologic basis for GBS, the role of the cellular and humoral systems in initiating the myelin breakdown has not been defined. In addition, the presence of antibodies against peripheral nerve in some patients with GBS may reflect a consequence rather than the cause of the pathologic lesions (31,32).

GBS is generally regarded as having a benign prognosis. Most patients have a spontaneous recovery without residual disability. However, the disease has been treated as a medical emergency requiring frequent monitoring of pulmonary vital capacity in order to identify patients requiring ventilatory assistance (17). At present there are no clinical criteria that can predict the clinical course, prognosis or outcome of GBS (33,34).

Until the present time, no identified treatment has altered the natural history of the disease. Supportive nursing care has been the mainstay of treatment. A multicenter randomized trial in the treatment of GBS by steroids demonstrated no benefit while suggesting potential harm, manifested by delayed recovery, in treated versus control, patients (14).

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In an uncontrolled series, five patients with GBS treated with azathioprine, after failing to respond to steroids, demonstrated clinical improvement within two weeks (35). It was not possible to determine if these apparent responses were spontaneous or treatment-related.

RATIONALE

The rationale for the application of apheresis to the treatment of GBS is derived from a number of factors. Proponents argue that by separating plasma fractions using apheresis they are able to separate and remove immunoglobulins and immune complexes from plasma. They further point to evidence that humoral mechanisms are responsible for the pathogenesis of the disease based on the demonstration that sera from patients with GBS contain myelinotoxic factors (36). Although the sera from a small percentage of control subjects (7.5 percent) was found to cause in vivo demyelination of rat sciatic nerves, almost 50 percent of sera from patients with GBS caused demyelination (37). Sera from 84 percent of another group of GBS patients produced demyelination of peripheral nerves in tissue culture (15).

This evidence, in addition to the proven benefit of apheresis in the treatment of chronic relapsing polyneuropathy, in which immune dysfunction is also thought to play some role, led to the formulation of a hypothesis (1). If serum factors were a significant factor in GBS, removal or dilution of these factors would have a favorable effect on the course of the disease (17). A trial of apheresis in the treatment of experimentally induced allergic neuritis in rabbits resulted in the development of a less severe form of the disease than in control animals (38).

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REVIEW OF THE LITERATURE

The first report of a trial of apheresis in the treatment of GBS was by Brettle et al. in 1978 (39). On the basis of evidence suggesting that a humoral component may be implicated in the pathogenesis of GBS, apheresis was tried in the case of a 22 year old woman with acutely deteriorating polyneuropathy. She underwent four successive daily plasma exchanges. After the second exchange there was dramatic improvement in limb strength. After the fourth exchange she could sit and stand unaided and continued to improve over a period of two weeks. This striking and abrupt improvement in a disease, where it is unusual to see spontaneous improvement before two weeks, prompted interest in further trials of this modality (40,41).

Schooneman, et al. reported "spectacular" results, (in nine of ten cases), within 24 hours after the first of a series of 3-5 plasma exchanges over a two week period (42). They reported that neurological progression of disease was also halted in 9 of 10 cases and no patient required tracheotomy or intubation.

Gross, et al. reported observations on four cases of GBS (43). Two of the patients were subjected to apheresis during a rapidly progressive phase of the disease, and showed a prompt and substantial recovery of function. The other two patients were plasma "exchanged" when their disease activity had reached a plateau. Only minor degrees of improvement were seen in these cases.

Dau, et al. summarized their experience with apheresis in the treatment of 13 patients with GBS (44). Seven of their thirteen patients exhibited clinical improvement within 48 hours after their first apheresis. Patients were treated over 2-3 weeks with four or five plasma exchanges of four litres each using purified protein fraction as the replacement solution.

Reporting on 12 consecutive patients with GBS treated by apheresis, Kennard, Newland, et al. failed to show any more than a marginally beneficial effect on the course of the disease as measured by improvement or arrested rate of deterioration (45). There

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was no undue delay in instituting these treatments following the onset of illness. The volume of each plasma exchange was approximately four liters in this series.

Treatment by apheresis was performed by Osterman, et al. in seven patients with GBS (27). The condition of three patients improved markedly, with a rapid regression of symptoms. One patient demonstrated partial improvement and three failed to improve. There were no apparent pretreatment clinical differences between the responders and the non-responders.

In a trial attempting to correlate response to treatment with serum IgG antibodies, Nyland, et al. treated 16 GBS patients with apheresis (46). Prior to treatment, antibodies were detected in sera of nine of the sixteen patients. Five patients showed marked improvement. Four patients showed partial improvement. Seven patients failed to improve. All patients who demonstrated clinical improvement had elevated serum titers of IgG antibodies which were reduced by the apheresis. No patient without pretreatment serum antibodies showed improvement. The impressions from this trial were supported by a report by Marconi, et al. in which nine of eleven patients with GBS demonstrated rapid improvement after one or two "exchanges" (40). Clinical improvement was associated with sharp decreases in serum and cerebrospinal fluid titers of IgG antibodies.

The first reported randomized controlled trial of apheresis in GBS was by Mendell, et al. in 1983 (47). The trial involved 12 patients treated by 9 plasma exchanges of 2-3 litres each over four weeks in combination with prednisone (to offset the possibility of antibody rebound). Analysis of the data revealed no significant difference in the treated group over the controls as measured by testing muscle strength.

Another randomized controlled trial of apheresis in GBS was conducted in seven neurological centers in England (36). The trial involved 14 patients treated with five "exchanges" of 3-4 litres of plasma each over 5-10 days. Patients were followed periodically for one year and compared to a group of 15 untreated controls. Treated patients failed to demonstrate any significant benefit (as measured by functional disability tests).

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Preliminary results from a large cooperative randomized trial in France were reported on 133 out of 183 patients (48). A favorable short-term effect was seen in the group of 70 patients treated with apheresis. Assessment was made by muscle strength score and the need for assisted ventilation. The determination of the long-term effects of treatment awaits further data analysis.

A recently completed controlled clinical trial of apheresis in the treatment of GBS has studied 245 severely ill patients in 20 institutions in the United States and Canada (49). The protocol involved 3-5 "exchanges" (200-250 cc/kg) in 7-14 days. Apheresis was shown to be beneficial in terms of clinical improvement seen at 4 weeks, reduced time to improve one clinical grade, and reduced time to independent walking within six months. Improvement at 4 weeks was seen in 59 percent of treated patients versus 39 percent of controls. The median time to improve one clinical grade in treated patients was 21 days shorter than controls. The median time on respirator was shortened by 24 days in treated patients. The median time to independent (unassisted) walking was shortened by 32 days for all treated patients and by 72 days for those requiring treatment by respirator. Apheresis was particularly effective for patients who received treatment within 7 days of onset of disease and for patients who required assisted ventilation after entry into the study.

DISCUSSION

Under ideal circumstances the rational treatment of a disease should derive from an understanding of its pathophysiology. In the case of GBS, the pathophysiology has not been elucidated despite evidence supporting the role of immune mechanisms causing demyelination of peripheral nerves. The natural history of untreated GBS includes fluctuations in clinical status and occasional dramatic spontaneous improvement. In addition, most patients experience full recovery without treatment. These facts have made the efficacy of clinical treatment for this condition difficult to evaluate.

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The mechanism of action of apheresis is non-specific and remains hypothetical. Apheresis is ideally applied in cases where there is a demonstrable circulating factor responsible for the disease (50). At present, specific immunopathogenic plasma constituents have not been isolated in patients with GBS (6). Demyelinating factors are present in the sera of most patients with GBS especially during the acute phase of the disease (24). However, their role in the cause of GBS remains controversial (22). The fact that the clearing of antibodies from the serum of some patients correlated with clinical improvement following apheresis might suggest, but does not prove, a causal role for circulating factors in producing disease activity (31).

Numerous case reports and a few randomized controlled clinical trials have shown both the effectiveness or lack thereof of apheresis in the treatment of GBS. The earlier clinical trials suffered from too small a sample to yield definitive results. The weight of evidence from the largest and most recent randomized trials demonstrate that in many cases, apheresis is beneficial in the acute phase of GBS. The reasons for the failure of apheresis to effect clinical improvement in all patients is not known. It may be related to the absence of specific circulating immune factors in some patients. Current proposals for clinical trials may identify subgroups of patients most likely to benefit from apheresis and to provide guidelines for its use (51). The role of apheresis for mildly affected patients with GBS has not been addressed in any clinical trial and remains undefined (52).

Although apheresis is not risk free, its widespread use in thousands of patients treated for a variety of diseases attests to its safety as a procedure. Patients are regularly monitored during the procedure by physicians and nurses. In a report describing 153 apheresis treatments, the morbidity was minor (nausea five percent, vomiting three percent, paresthesias seven percent, urticaria three percent, transient hypotension eleven percent). None of these cases required the procedures to be terminated because of these reactions (53).

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A Federal Register notice of this assessment elicited no public response (54).

The practice committee of American Academy of Neurology conducted an evaluation of apheresis in the treatment of GBS and determined, in February 1983, that it is an "investigational technique".

The American Medical Association, through their division of Drugs and Technology has informed the Office of Health Technology Assessment (OHTA) that, "Plasmapheresis has been applied to this disease entity with apparent success. However, this syndrome shows such a high degree of spontaneous improvement that no definitive statement concerning the clinical efficacy of therapeutic plasma exchange (TPE) can be made at present. Two controlled clinical trials presently in progress hope to answer the question of efficacy."

The National Institutes of Health (NIH) has informed OHTA, in June of 1985, that the weight of evidence indicates that plasmapheresis probably shortens the course of the disease and speeds recovery from paralysis. The benefits of plasmaphersis appear to be most marked in individuals whose condition is deteriorating to the extent that they require respirator support. The NIH concludes that there is clear evidence to support the use of plasmapheresis in acute Guillain-Barre patients who are rapidly deteriorating and require respirator support. The benefit of plasmapheresis in less severely affected individuals is less clear.

The Food and Drug Administration has stated that the commercially available centrifugai cell separators used in apheresis procedures were developed prior to the enactment of the Medical Device Amendments and were not within the realm of their review. Membrane-type apheresis devices were not commercially available prior to the enactment of the Medical Device Amendments. By statute, membrane devices are classified into class III and require a premarket approval application (PMA) to be filed with FDA before the device is made commercially available. To date, five PMA applications have been approved by FDA which include the filters for therapeutic apheresis. These five membrane-type separators are approved as safe and effective for

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use in plasma separation.

The equipment which controls the blood pressure and flow rate during the therapeutic procedure has been found to be substantially equivalent to class II medical devices. To date, four 510(k) applications have been reviewed by FDA for the equipment used with apheresis membranes for therapeutic apheresis.

SUMMARY

Apheresis is a technique which permits the selective removal of plasma or other blood components from the circulation using cell separation, semipermeable membranes or affinity columns. The theoretical basis for the application of apheresis to the treatment of Guillain-Barre syndrome appears attractive and its safety has been well documented.

Until the present time no identified treatment has been demonstrated to alter the natural history of the Guillain-Barre syndrome. Clinical trials using steroids have resulted in either no benefit or potential harm in treated patients. Since 1978 a large and growing number of case reports as well as one prospective series have appeared in the clinical literature suggesting that apheresis was beneficial in some patients with GBS.

Recent data from large randomized clinical trials have clearly shown beneficial effects of apheresis in the acute phases of GBS when applied early after the onset of disease. The weight of evidence and preponderance of clinical opinion support the use of apheresis for the treatment of patients with GBS, who are severely ill or deteriorating. Treatment must be instituted as early as possible in order to optimally reduce morbidity and mortality caused by this disease.

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Prepared by: Harry Handelsman, D.O.

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16. Abstract (Limit: 200 words)
Apheresis is a procedure which employs a blood processing machine to selectively remove plasma or other blood components from the circulation. It is most often used to collect donor platelets or leucocytes. It has been successful in the treatment of some auto-immune diseases. Apheresis has been investigated in the treatment of a number of diseases presumed to be immunologically mediated. Clinical and experimental evidence have suggested that circulating humoral factors are responsible for the pathogenesis of Guillain-Barre syndrome. Studies suggest that the removal or dilution of these factors by apheresis would have a favorable effect on the clinical course of the disease. No previous treatment has been demonstrated to alter its natural history. Numerous case reports and data from a recently completed multicenter trial of apheresis have shown beneficial effects in the acute phases of the disease. Apheresis was particularly effective when applied within 7 days of disease onset and for patients who required assisted ventilation.

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